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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,738	11/12/2003	John Hilfinger	TSR-10002/38	7532

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,738	HILFINGER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-24,26,27 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-24,26,27 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was filed on 7/17/06. Claims 25, 28, and 29 were canceled. Claims 8-24, 26, 27, and 30 remain pending and are under consideration. Rejections not reiterated from the previous Office Action are withdrawn.

Specification

The amendment filed 7/17/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Page 19 of the specification has been amended to recite "deficiencies in... cancer [line 6 of the amendment],... clotting factors [line 12],... bone diseases [line 17],... myasthenia gravis", (line 18). The specification as filed did not disclose the treatment of deficiencies in cancer, deficiencies in clotting factors as broadly recited, or deficiencies in bone diseases. Further, the amendment to the paragraph beginning on page 9, line 15 introduces new matter into the specification. This amendment changes the originally filed definition of 'A-R_1' into a definition of 'R_1'. However, the specification as filed did not define R_1 in the absence of A, instead it defined A-R_1 as "a cholesterol derivative; a C_8-C_{24} alkyl; C_8-C_{24} heteroatom substituted alkyl wherein the heteroatom is O, N or S". A review of the specification did not reveal any support for applying this definition solely to R_1, instead of to the combination A-R_1. Applicant did not point to any support for this amendment in the response filed 7/17/06. Also, this paragraph has been amended to

recite "ursoldeoxycholic acid". There is no apparent support for this term in the specification as filed, or the prior art. Applicant may have intended "ursodeoxycholic acid" instead, but there is no apparent support for that term in the specification as filed either.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

Claim 18 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 18 depends from claim 8, and requires that "said A is a hydrophilic moiety." However, claim 8 already specifies that "A is a hydrophilic moiety".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 8-24, 26, 27, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as filed defines A-R_1 at page 9 as "a cholesterol derivative; a C_8-C_{24} alkyl; C_8-C_{24} heteroatom substituted alkyl wherein the heteroatom is O, N or S; where A is a hydrophilic moiety A that illustratively includes C_0-C_4 alkyl-hydroxy, -substituted amino, -quaternary amino, -sulfonate, -phosphonate, and -carboxylate; and targeting ligand." From this definition, it appears that A can be -sulfonate, -phosphonate, or targeting ligand only when A-R_1 is a cholesterol derivative, because the other A-R_1 entities (C_8-C_{24} alkyl; C_8-C_{24} heteroatom substituted alkyl wherein the heteroatom is O, N or S) do not allow for -sulfonate, -phosphonate, or targeting ligand 'A' groups. However, the claims as amended now allow for -sulfonate, -phosphonate, and targeting ligand 'A' groups to be attached to C_8-C_{24} alkyl and C_8-C_{24} heteroatom substituted alkyl R_1 groups. The specification as filed does not support this embodiment, so the claims recite new matter.

Further, the claims now define R_1 as a cholesterol derivative; a C_8-C_{24} alkyl; C_8-C_{24} heteroatom substituted alkyl wherein the heteroatom is O, N or S; or a bile acid. However, the specification as filed did not define R_1 in the absence of A, instead it defined A-R_1 as "a cholesterol derivative; a C_8-C_{24} alkyl; C_8-C_{24} heteroatom substituted alkyl wherein the heteroatom is O, N or S". A review of the specification did not reveal any support for the amendment and Applicant did not point to any in the response filed 7/17/06. As a result, the claims as amended recite new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 10, 13-18, 20, 23, 24, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Gebeyehu et al (US Patent 6,075,012).

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of R-A-Z, wherein R can be cholic acid, A is -NH-CH_2-, and Z can be a polycationic peptide such as a protamine, a histone, or a nucleic acid binding protein. See column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-56; and column 9, line 58 to column 10, line 10. Thus Gebeyehu anticipates embodiments of the instant claims requiring A-R_1-Q-Y-Z wherein:

A is a hydroxyl group of cholic acid,

R_1 is a cholesterol derivative that is cholic acid minus the 'A' hydroxyl group, and with the CH_2- of the -NH-CH_2- group of Gebeyehu attached,

Q is the NH of the -NH-CH_2- of Gebeyehu, and

Y and Z are accounted for by the polycationic peptide of Gebeyehu.

Although Gebeyehu taught cholic acid, claims 21 and 22 are not included in this rejection. This is because of the requirement for attachment of a hydrophilic group 'A' to the cholic acid. This would require addition of a group other than the hydrophilic hydroxyl groups already contained within cholic acid. Gebeyehu does not teach this.

Gebeyehu taught that the compositions could be used to transfect subject cells in vivo and in vitro for research purposes with DNA or RNA encoding expressible proteins or ribozymes. See paragraph bridging columns 11 and 12. The composition could comprise other compounds, such as viral envelope peptides, cationic lipids, and chloroquine. Absent evidence to the contrary, these are considered to be therapeutic compounds , and the viral peptides are considered to be antigenic.

Gebeyehu also taught kits comprising the compositions. See column 13, lines 18-24.

Claims 8, 13, 14, 17, 18, 20, 23, 24, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Stupp et al (US Patent 5,932,539).

Stupp taught a biodegradable polymer of the general formula L- P- T wherein L is a lipophilic membrane binding moiety such as a cholesterolyl moiety, P is a divalent peptide linker, and T is a polyionic organic group such as polylysine, and its use to delivery nucleic acids in vivo. See claim 1, column 6, lines 25-32, and sentence bridging columns 6 and 7. Thus Stupp anticipates embodiments of the instant claims requiring A-R_1-Q-Y-Z wherein

A is the hydroxyl group of cholesterol,

R_1 is a cholesterol derivative that is cholesterol without its hydroxyl group,

Q is either the N or O terminus of the peptide linker

Y is the rest of the peptide linker, and

Z is polylysine.

For claims 8, 13, 14, 17, and 18, requiring only A-R_1-Q-Z, Z is accounted for by the combination of the peptide linker and the polylysine.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gebeyehu et al (US Patent 6,075,012).

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of R-A-Z, wherein R can be cholic acid, A is -NH-CH_2-, and Z can be a polycationic peptide such as a protamine, a histone, or a nucleic acid binding protein. See column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-56; and column 9, line 58 to column 10, line 10. Thus Gebeyehu anticipates embodiments of the instant claims requiring A-R_1-Q-Y-Z wherein:

A is a hydroxyl group of cholic acid,

R_1 is a cholesterol derivative that is cholic acid minus the 'A' hydroxyl group, and with the CH_2- of the -NH-CH_2- group of Gebeyehu attached,

Q is the NH of the -NH-CH_2- of Gebeyehu, and

Z is accounted for by the polycationic peptide of Gebeyehu.

Gebeyehu did not explicitly teach a commercial package comprising the composition and instructions for use. However, Gebeyehu did teach kits comprising the compositions. See column 13, lines 18-24. it would have been obvious to one of ordinary skill in the art at the time of the invention to place the components of the kit of Gebeyehu into a container. One would have been motivated to do so in order to organize the components into an easily retrievable state. One would have been motivated to include instructions because one of ordinary skill in the art appreciates that referring to instructions decreases the frequency of errors. Thus the invention as a whole was prima facie obvious.

Claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gebeyehu et al (US Patent 6,075,012) as applied to claims 8 and 30 above, and further in view of Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002).

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of R-A-Z, wherein R can be cholic acid, A is -NH-CH_2-, and Z can be a polycationic peptide such as a protamine, a histone, or a nucleic acid binding protein. See column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-56; and column 9, line 58 to column 10, line 10. Thus Gebeyehu anticipates embodiments of the instant claims requiring A-R_1-Q-Y-Z wherein:

A is a hydroxyl group of cholic acid,

R_1 is a cholesterol derivative that is cholic acid minus the 'A' hydroxyl group, and with the CH_2- of the -NH-CH_2- group of Gebeyehu attached,

Q is the NH of the -NH-CH_2- of Gebeyehu, and

Z is accounted for by the polycationic peptide of Gebeyehu.

Gebeyehu did not teach oral delivery, or secretion of an expressed protein.

Perrie taught oral intragastric delivery of cationic liposome comprising nucleic acids encoding hepatitis B surface antigen (HbsAg). DNA vaccines encoding HbsAg were formulated with cationic lipids (DOTAP) and administered orally. Immune responses against the antigen were observed. See abstract. HbsAg is a surface protein, and so is expressed and routed through the secretory pathway. Also, generation of an immune response requires presentation of the antigen on a cell surface, again requiring secretion.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cationic lipid of Gebeyehu in the method of Perrie. Gebeyehu taught that the lipid could be substituted for, or added to, such cationic lipids as DOTAP. See column 5, lines 37-51; and column 16, lines 18-22. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. Thus the invention as a whole was prima facie obvious.

Claims 10-12 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gebeyehu et al (US Patent 6,075,012) as applied to claims 8 and 30 above, and further in view of Kitadai et al (Brit. J. Cancer 81(14): 647-653, 1999).

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of R-A-Z, wherein R can be cholic acid, A is -NH-CH_2-, and Z can be a polycationic peptide such as a protamine, a histone, or a nucleic acid binding protein. See column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-56; and column 9, line 58 to column 10, line 10. Thus Gebeyehu anticipates embodiments of the instant claims requiring A-R_1-Q-Y-Z wherein:

A is a hydroxyl group of cholic acid,

R_1 is a cholesterol derivative that is cholic acid minus the 'A' hydroxyl group, and with the CH_2- of the -NH-CH_2- group of Gebeyehu attached,

Q is the NH of the -NH-CH_2- of Gebeyehu, and

Z is accounted for by the polycationic peptide of Gebeyehu.

Gebeyehu did not teach secretion of an expressed protein, expression of an interleukin, or a gastrointestinal target cell.

Kitadai taught transfection of human gastric carcinoma cells with an expression vector encoding the secreted protein interleukin-8. Transfection was performed using the cationic lipid formulation LIPOFECTIN (DOTMA/DOPE).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cationic lipid of Gebeyehu in the method of Kitadai. Gebeyehu

taught that the lipid could be substituted for, or added to, such cationic lipids as DOTMA and DOPE. See column 5, lines 37-51; column 6, lines 32-38; and column 16, lines 18-22. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. Thus the invention as a whole was prima facie obvious.

Prior Art Made of Record but not Relied Upon

Niedzinski et al (Lipids 35(7): 721-727, 2000) taught cholic acid conjugates comprising two different DNA binding domains, their use to protect DNA from degradation in the gastric system, and their use to deliver plasmids to NIH 3T3 cells in vitro. The DNA binding domains of Niedzinski were not peptides, however, many peptidyl DNA binding domains were known in the prior art, and Niedzinski noted that the cholic acid imidazole intermediate used to make the subject molecules should be adaptable to the synthesis of a variety of conjugates. One of ordinary skill in the art appreciates that these would include polycationic peptides.

Request for Interview

At page 12 of the response, Applicant set forth a request for an interview with the Examiner and in the event that the application was not found to be in condition for allowance. This request was attached to an amendment which must be acted on by the Office in a timely fashion. In the future, Applicant is invited to contact the Examiner directly to arrange any interviews prior to the submission of amendments, so that any remaining issues can be discussed in a timely fashion.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
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